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14. ABSTRACT

In Year 2 of this award we examined whether duraplasty after acute thoracic spinal cord injury (SCI) in a porcine model could improve long-term functional outcome after injury. We finalized the 12-week PTIBS analysis as well as the somatosensory-evoked potentials, which was recorded at baseline, 3 hours post injury and at the final week of the study (12 weeks post SCI). Our data suggest that duraplasty surgery might improve functional recovery early after SCI compared to SCI-animals without duraplasty. In Year 2 we also started surgeries as part of Aim 2 to determine if surgically expanding the subarachnoid space with a duraplasty will alter intraparenchymal spinal cord pressure, SCBF, and metabolic responses; monitored over a 7-day period. During these surgeries, we inserted a total of six probes into the spinal cord in order to be able to measure the blood flow/oxygenation, pressure and microdialysis responses distal proximal (2 mm) and (22 mm) to the impact site. The data are too preliminary for one to draw firm conclusions. Additional surgeries will be performed in YEAR 3 of the grant.

15. SUBJECT TERMS

Spinal Cord Swelling, Hydrostatic Pressure, Duraplasty, Spinal Cord Injury, Pressure Reactivity Index

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TABLE OF CONTENTS

1 INTRODUCTION

After acute spinal cord injury (SCI) the spinal cord is frequently found to have swollen dramatically, particularly after it has been surgically decompressed. In traumatic brain injury (TBI), brain swelling and increases in intraparenchymal pressure are routinely considered in both the surgical and hemodynamic management of such patients. However, this swelling has largely been neglected in SCI, despite being consistently observed. Even after surgical decompression, such swelling may result in the cord being subjected to significant pressure, either due to constriction by the pia mater, the dura mater, or both. The physiologic consequences of this are poorly understood, and many fundamental questions remain about its impact on intraparenchymal pressure, spinal cord perfusion, and downstream metabolic responses. Determining the physiologic/biologic consequences of this swelling and how they can be mitigated to reduce secondary injury will guide the optimal clinical management of acute SCI. As an example of how swelling, increased intraparenchymal pressure, and its effects on perfusion are factored into clinical decision-making, TBI investigators have established the Pressure Reactivity Index (PRx) to identify where autoregulation remains intact and to guide optimal perfusion support based on that. The PRx has not been investigated in SCI, but given that the cord also swells and has impaired autoregulation, it is likely applicable here as well. This promising approach opens the possibility that we could individualize and optimize the hemodynamic support of acute SCI patients in order to support perfusion without exacerbating deleterious increases in intraparenchymal pressure.

2 KEYWORDS

- Spinal Cord Swelling
- Hydrostatic Pressure
- Spinal Cord Injury
- Pressure Reactivity Index
- Porcine model of SCI

3 ACCOMPLISHEMENTS

3.1 Protocol and Activity Status

- **Human Use Regulatory Protocols**

No human subjects research will be performed to complete the Statement of Work

- **Use of Human Cadavers for RDT&E, Education or Training**

No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work

- **Animal Use Regulatory Protocols**

  Total Protocols: 1 animal use research protocol will be required to complete the Statement of Work

- **Protocol:** 1 of 1
- **Protocol [ACURO Assigned Number]:** SC130008
- Title: **SCI in pigs** [IACUC protocol number A13-0013]
- **Target required for statistical significance**: n=6/group
- **Target approved for statistical significance**: n=6/group
- **Submitted to and Approved by:** Bryan K. Ketzenberger, DVM, DACLAM
- **Status: approved** 26-MARCH-2015

3.2 Approved Statement of Work

The approved statement of work is described below. A Gantt chart is provided in Table 1 for reference (see page 5).

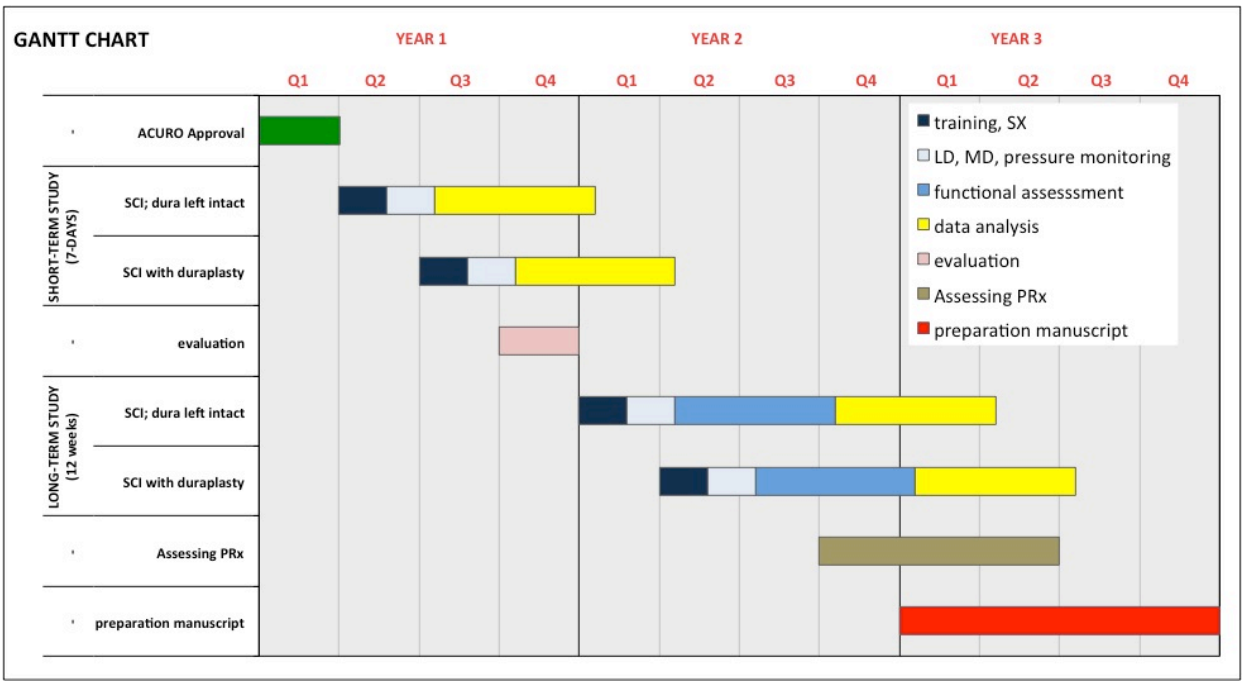
Specific Aim 1: Evaluate if compression by the surrounding dura produces increased intraparenchymal pressure within the injured, swollen cord.	**Months**	**Site**
Subtask 1: Submit documents for ACURO approval	1-3	UBC
Milestone(s) Achieved: Obtain ACURO approval	3	
Subtask 2: Characterize the CSF pressure changes for 7-days after SCI and decompression	3-13	UBC
Subtask 3: Characterize the cord intraparenchymal pressure changes for 7-days with probes positioned in close proximity of the epicenter and a more distal segment (control)	3-13	UBC
Milestone(s) Achieved: Characterization of spatial and temporal hydrostatic pressure changes in the epidural space and spinal cord after SCI and decompression (without dural decompression)	10-15	

Specific Aim 2: To evaluate if dural compression contribute to progressive deficit in blood perfusion and contribute to the pathophysiology of secondary damage after traumatic SCI	**Months**	**Site**
Subtask 1: Characterize the metabolic and spinal cord blood flow (SCBF) changes for 7-days with probes positioned in close proximity of the epicenter and a more distal segment (control)	6-18	UBC
Subtask 2: Determine the effects of surgically opening the dura and expanding the subarachnoid space with a duraplasty will alter intraparenchymal spinal cord pressure, SCBF, and metabolic responses	6-18	UBC
Subtask 3: Examine the histopathological changes in the harvested spinal cord at the 7-day time point	12-18	UBC
Milestone(s) Achieved: Definition of any relation between changes in systemic pressure and SCBF when the spinal cord is decompressed with or without opening of the overlying dura.	18-24	

Specific Aim 3: Evaluate behavioral recovery for a total of 12 weeks following SCI with or without duraplasty	**Months**	**Site**
Subtask 1: Assess hindlimb motor function during overground ambulation (PTIBS)	12-32	UBC
Subtask 2: Neurophysiologic monitoring with transcranial motor-evoked potentials	12-32	UBC
Milestone(s) Achieved: Definition of any relationship between functional recovery after spinal cord decompression with or without dural decompression; preparation of manuscript	32-36	

Specific Aim 4: Evaluate if a moving correlation index exists between mean arterial blood pressure and CSF/cord pressure (pressure reactivity index; PRx)	**Months**	**Site**
Subtask 1: Determine the temporal profile of spinal cord autoregulation following SCI during the first 7-days after SCI	21-30	UBC
Subtask 2: identify any variables - blood pressure, spinal cord perfusion, intraparenchymal pressure, or CSF pressure - associated with impairment or preservation of PRx	21-30	UBC
Milestone(s) Achieved: Quantification of any relation between arterial blood pressure or spinal cord perfusion and CSF pressure; preparation of 1-2 peer reviewed papers	30-36	UBC

Table 1. Approved statement of work (Gantt Chart)



3.3 Current Progress on Statement of Work

A Gantt chart of the current work is provided in Table 2 for reference (page 7). The months in the approved statement of work do not necessarily match with the Gantt chart, since the Gantt chart reflects actual work completed in each year.

Aim 1: Evaluate if compression by the surrounding dura produces increased intraparenchymal pressure within the injured, swollen cord.

- **Task 1:** Submit documents for ACURO approval

  Completed. *ACURO approval was granted 26-MARCH-2015.*

- **Task 2:** Characterize the CSF pressure changes for 7-days after SCI and decompression

  Completed.

- **Task 3:** Characterize the cord intraparenchymal pressure changes for 7-days with probes positioned in close proximity of the epicenter and a more distal segment (control)
-

  Completed.

Aim 2: To evaluate if dural compression contribute to progressive deficit in blood perfusion and contribute to the pathophysiology of secondary damage after traumatic SCI (7-day evaluation)

- **Task 1:** Characterize the metabolic and spinal cord blood flow (SCBF) changes for 7-days with probes positioned in close proximity of the epicenter and a more distal segment (control)

  In progress.

- Task 2: Determine the effects of surgically opening the dura and expanding the subarachnoid space with a duraplasty will alter intraparenchymal spinal cord pressure, SCBF, and metabolic responses

  In progress.

- Task 3: Examine the histopathological changes in the harvested spinal cord at the 7-day time point

  In progress.

Aim 3: Evaluate behavioral recovery for a total of 12 weeks following SCI with or without duraplasty

- **Task 1:** Assess hindlimb motor function during overground ambulation (PTIBS)

  Completed.

- **Task 2:** Neurophysiologic monitoring with transcranial motor-evoked potentials

  Completed.

Aim 4. Evaluate if a moving correlation index exists between mean arterial blood pressure and CSF/cord pressure (pressure reactivity index; PRx)

- **Task 1:** Determine the temporal profile of spinal cord autoregulation following SCI during the first 7-days after SCI

  In progress

- **Task 2:** identify any variables - blood pressure, spinal cord perfusion, intraparenchymal pressure, or CSF pressure - associated with impairment or preservation of PRx

  In progress

Table 2: Gantt chart of current work. The Gantt chart reflects actual work completed. Therefore, months in the approved statement of work do not necessarily match with the Gantt chart, since the Gantt chart reflects actual work completed in each year.

Specific Aim 1+2: *7-day Evaluation of Duraplasty evaluation* 1a. Dura intact (n=6) 1b. Duraplasty (n=6)	**YEAR 1**				**YEAR 2**				**YEAR 3**			
Task:	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
1. ACURO Approval												
2. Animal training / Surgery												
3. Spinal cord monitoring of pressure, oxygenation, SCBF and microdiaysis												
4. Histologic assessments												
5. Data Analysis / Dissemination												
Specific Aim 3: *12-week Evaluation of Duraplasty* 1a. Dura intact (n=6) 1b. Duraplasty (n=6)	**YEAR 1**				**YEAR 2**				**YEAR 3**			
Task:	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
1. Animal training / Surgery												
2. Behavioral / functional assessments												
3. Histologic assessments												
4. Data Analysis / Dissemination												
Specific Aim 4: *Evaluate if a moving correlation index exists between mean arterial blood pressure and CSF/cord pressure (pressure reactivity index; PRx)*	**YEAR 1**				**YEAR 2**				**YEAR 3**			
Task	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
1. Determine the temporal profile of spinal cord autoregulation following SCI during the first 7-days after SCI												
2. Identify any variables - blood pressure, spinal cord perfusion, intraparenchymal pressure, or CSF pressure - associated with impairment or preservation of PRx												

4 OVERALL PROJECT SUMMARY

Human SCI is typically caused by a combination of high velocity contusion followed by sustained mechanical compression. Relieving this 'extrinsic' mechanical compression in a timely manner intuitively would seem to be neuroprotective and result in improved neurologic function. However, the cord itself then undergoes considerable post-decompression swelling as demonstrated in SCI-patients. The spinal cord may ultimately swell to the point where it compresses against the dura, resulting in increased intraspinal pressure at the injury site as demonstrated by Papadopoulos and colleagues (2004). Such swelling and rise in the pressure within the spinal cord has also been observed in our porcine model of SCI (Figure 1 & 2). This suggests that we can utilize this model to investigate what is happening within the spinal cord during this swelling. When the cord swells against the dura, there may be an increase in pressure and reduction in spinal cord perfusion (as suggested by Papadopoulos et al.) **Our research question is: would it be beneficial to decompress the spinal cord by opening the dura and enlarging the subarachnoid space?** (as shown in Figure 3)

Figure 1: The swollen cord expands against the dura within hours after decompression. Prior to injury, the subarachnoid space is clearly seen between the spinal cord and dura. After SCI and within 10 min of decompression, residual deformation of the cord is observed. As inflammatory responses in the cord ensue, and the swelling cord fills the subarachnoid space, the cord pushes up against the dura within 5 hours of decompression (Jones et al., 2012).

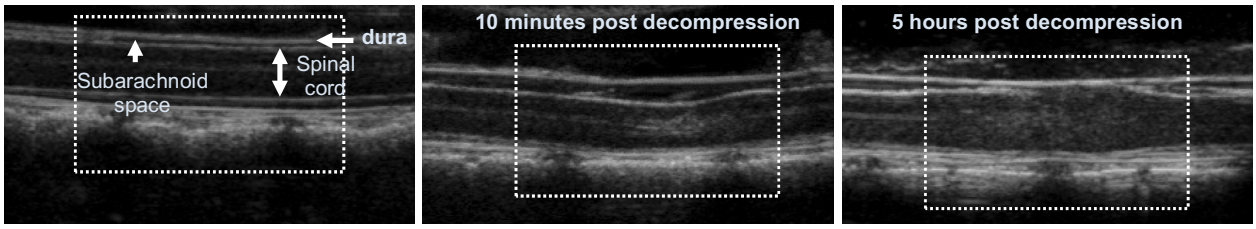


Figure 2: Monitoring of hydrostatic spinal cord pressure in acute SCI using a porcine model. (A) Surgical set-up to measure hydrostatic pressure within the spinal cord for 7 days. Three probes for monitoring oxygenation and blood flow, hydrostatic pressure and microdialysis were inserted through the dura and into the spinal cord 1.2 and 3.2 cm caudal to the injury. The recording wires from each probe were brought out of the surgical field, tunnelled through the skin and collected along the back of the animal. **(B)** At the injury site (1.2-cm) contusion injury followed by compression (grey shading) resulted in high intraparenchymal pressure. Following decompression intraparenchymal spinal cord pressure drops, after which it rises again remaining high for days, which suggests considerable post-SCI swelling. Such increases in cord pressure were also observed as far as 3.2-cm away from the trauma site.

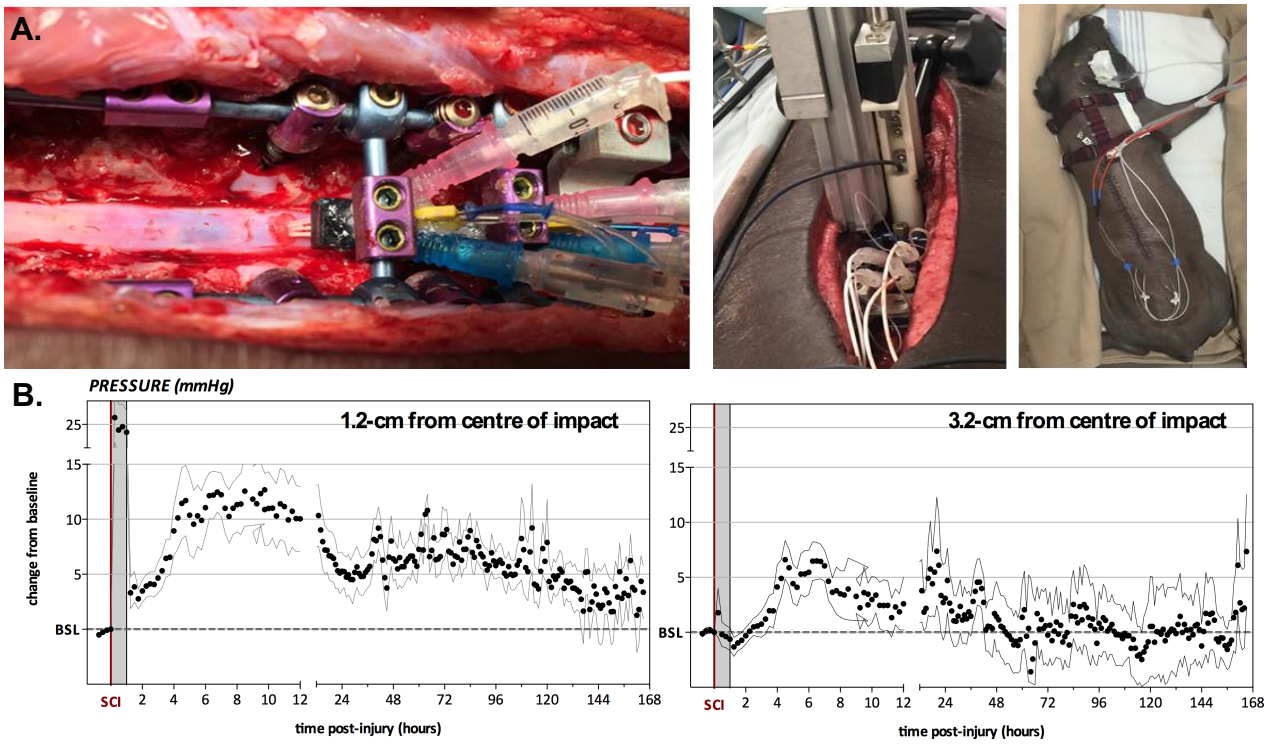
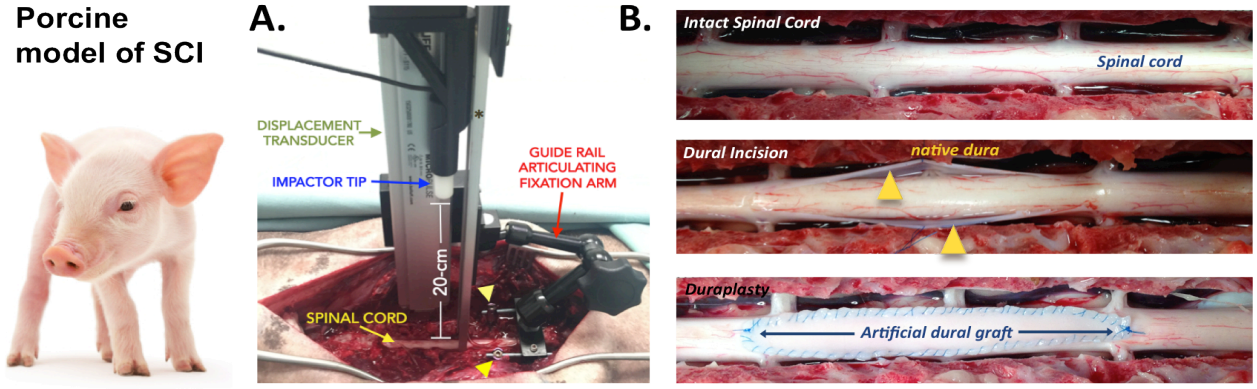


Figure 3: Understanding the effect of relieving spinal pressure after SCI through duraplasty. (A) Following a T10 dorsal spinal contusion injury and **(B)** C6-T13 transverse dural incision, a 10x1 cm artificial dural graft (Medtronic, US) was sutured to the remaining dura mater and sealed with fibrin glue. Control animals received an identical spinal cord contusion, however without expansile duraplasty.



4.1 Results

Aim 3, Task 1 & 2: Assessment of behavior and functional consequences of SCI with or with duraplasty using the Porcine Thoracic Injury Behavioral Scale (PTIBS) and neurophysiologic testing.

We finalized the 12-week PTIBS analysis as well as the somatosensory-evoked potentials, which was recorded at baseline, 3 hours post injury and at the final week of the study (12 weeks post SCI). Twelve female Yucatan pigs, weighing 20-25 kg, were used. The animals were randomly divided into two groups (n=6 per group); the first group underwent contusion/compression SCI followed by duraplasty surgery and the second group comprised the SCI controls (no duraplasty).

Method: An incision was made in the skull at the coronal and sagittal sutures. Four screws were inserted at 10mm away from each suture. Sub-dermal needle electrodes were placed in the toes of the hind limbs and the right forelimb. A baseline Ephys measurement was done to measure SSEPs and MEPs. Laminectomy was carried out at T6 to T10 levels. A second baseline Ephys measurement was done right before injury to ensure no differences had taken place during the laminectomy. Weight drop injury was conducted at the T10 using a 50g weight from a 20cm height followed by 5 minutes of compression using 150g. Immediately after decompression, a post-injury Ephys measurement was taken. An artificial dura graft was then sutured onto the dura of half of the animals (n=6 per group). The non-duraplasty group had their CSF removed to mimic the escape of CSF during duraplasty suturing. Another Ephys measurement was done at 3 hours post injury (after duraplasty) before the animal was closed and recovered. Behavioral testing was performed weekly up to 12 weeks post-injury using the Porcine Thoracic Injury Behavior Scale, a 10-point scale, with 1-3 describing hindlimb movements without weight support and 4-10 describing varying increasing degrees of stepping and postural ability. At the 12-week time point, also a last Ephys measurement was taken.

Table 1. Experimental information and current status of the animals

ID	Name	Species	SX date	Injury Specifics	Force (kdyn)	Weight (kg)	Treatment	Status
7753	Archery	Yucatan	20-Jul-15	**Contusion:** 50gr/20cm **Compression:** 150gr/5min	2950	21.5	duraplasty	Completed
7762	Bocce	Yucatan	20-Jul-15		2409	20.5	SCI only	Completed
7731	Curling	Yucatan	21-Jul-15		2976	19.0	duraplasty	Completed
7721	Darts	Yucatan	21-Jul-15		2170	20.5	SCI only**	Completed
7732	Equestrian	Yucatan	22-Jul-15		2014	18.5	duraplasty	Completed
7743	Football	Yucatan	22-Jul-15		3482	18.5	SCI only	Completed
7730	Golf	Yucatan	29-Jul-15		3132	19.5	duraplasty	Completed
7751	Hockey	Yucatan	29-Jul-15		2935	20.0	SCI only	Completed
7736	Ice Skating	Yucatan	4-Aug-15		2907	19.0	duraplasty	Completed

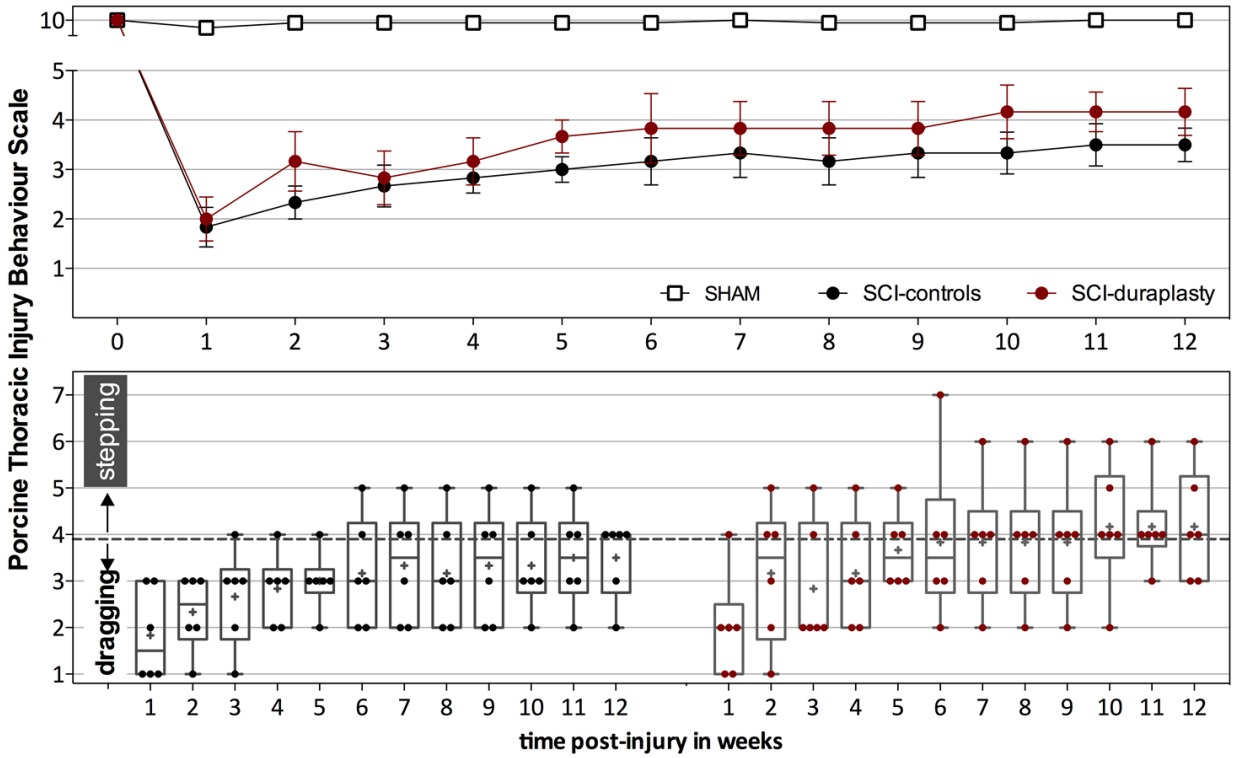
7744	Judo	Yucatan	4-Aug-15		2681	19.5	SCI only	Completed
7758	Karate	Yucatan	5-Aug-15		3047	21.5	duraplasty	Completed
7759	Lacrosse	Yucatan	5-Aug-15		2388	19.0	SCI only**	Completed
7800	Marathon	Yucatan	19-Aug-15			25.0	SCI only	Completed
7791	Noodling	Yucatan	19-Aug-15		2145	24.0	SCI only	Completed

** Heath complications. Animal had to be euthanized before end of experiment

Results:

PTIBS. Animals in both the SC-control and SCI-duraplasty group demonstrated behavioral recovery over time. In our study, most SCI-control animals (84%) showed hindlimb dragging (PTIBS score of 1-3) up to 5 weeks post-injury (Figure 4). However within the first week after SCI, half of the animals that received a duraplasty after SCI (50%) were already capable of weight-supported rhythmic hindlimb movements or making some steps (PTIBS ≥ 4). No differences were found at the end of study (12 weeks) between the SCI animals, which received duraplasty surgery versus the SCI control group.

Figure 4: Behavioural recovery is improved in the majority of the animals early after duraplasty surgery. (Top) average PTIBS per group, (Bottom) each dot represents an individual animal. On each box, the central line marks the median, the edges of the box mark the 25th and 75th percentiles, and the whiskers mark the most extreme data points not considered outliers.



Somatosensory-evoked potentials. Independent of the intervention group (SCI with or without duraplasty), both left and right hind limb SSEP amplitude was virtually absent acutely after SCI and showed no recovery at 12 weeks following injury (no assessment was performed between 3-hrs and 12 weeks post-SCI) (Figure 5). The abolished hindlimb SSEP is likely due a complete interruption of the ascending sensory pathways from the peripheral nerves to the somatosensory cortex due to the extensive thoracic spinal cord damage produced by the primary contusive SCI, hemorrhage, and the secondary injury mechanism. There was no difference in recovery of hindlimb SSEP amplitude between the groups.

In both groups forelimb SSEPs are significantly increased in amplitude after 12 weeks (Figure 6). The significant increase in amplitude could potentially be explained by cortical reorganization, which is evident in rodent models and humans with SCI. There was no difference in recovery of forelimb SSEP amplitude between the groups.

Figure 5: Left and right hindlimb somatosensory evoked potentials (SSEPs). Note: Abolished lower limb SSEP amplitude after SCI.

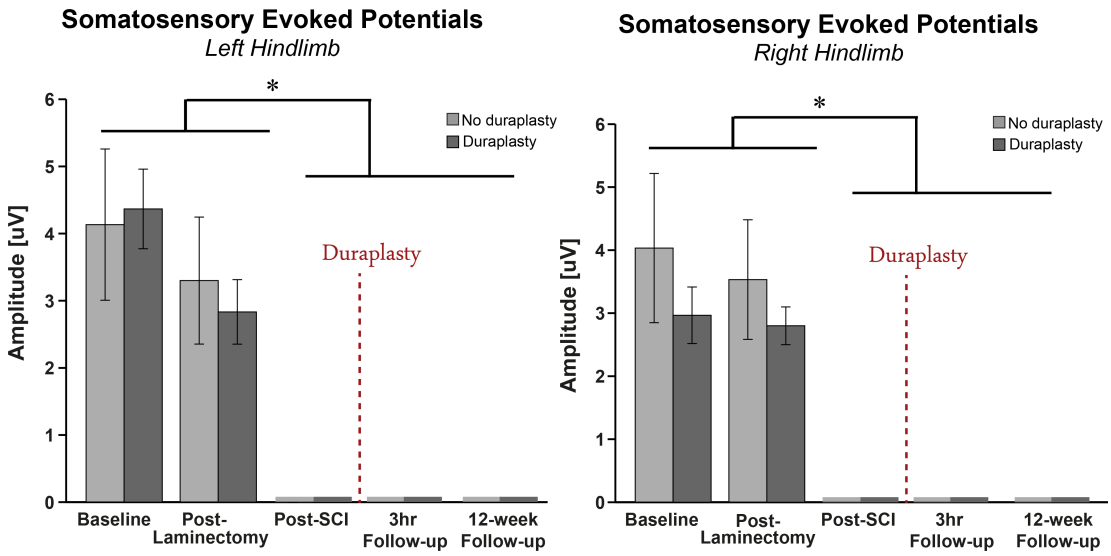
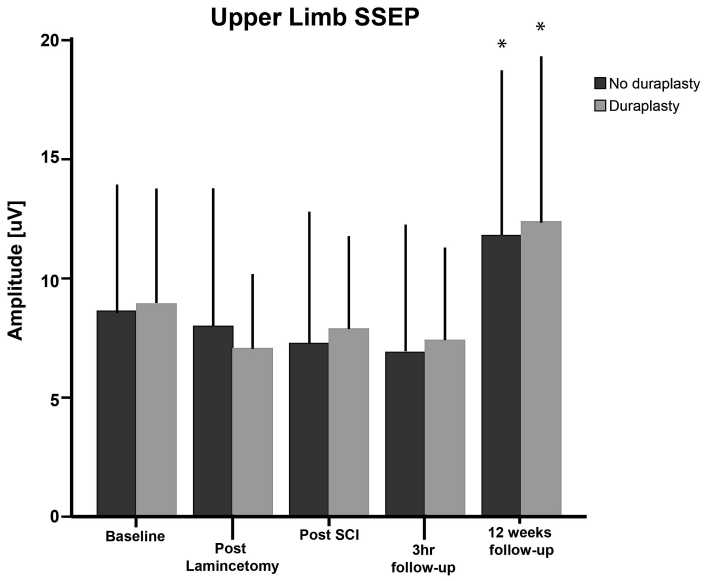


Figure 6: Upper limb somatosensory evoked potentials (SSEPs). Note: Increased upper limb SSEP amplitude 12 weeks post injury.



In summary, our results demonstrate a tendency towards an improved functional recovery (based on PTIBS) for the majority of the SCI-duraplasty animals in the acute period after SCI (within 5 weeks). Additionally we show an increased in forelimb SSEPs suggesting that the brain may employ compensatory mechanisms to make up for the loss of hindlimb function.

Aim 2, task 1-3: To evaluate if dural compression contribute to progressive deficit in blood perfusion and contribute to the pathophysiology of secondary damage after traumatic SCI (7-day evaluation)

In Year 2 we performed surgeries as part of **Aim 2** to determine if surgically expanding the subarachnoid space with a duraplasty will alter intraparenchymal spinal cord pressure, SCBF, and metabolic responses; monitored over a 7-day period. During these surgeries, we insert a total of six probes into the spinal cord in order to be able to measure the blood flow/oxygenation, pressure and microdialysis responses distal proximal (2 mm) and (22 mm) to the impact site. As a consequence we need to perform the duraplasty procedure before the probe insertion as well as the actual weight drop.

Methods:

The methodologic challenge imposed by having to perform the duraplasty procedure before probe insertion and weight drop is to create the biomechanically equivalent injury between the duraplasty animals and control, non-duraplasty animals. By expanding the subarachnoid space with the duraplasty, there is potentially more CSF within the

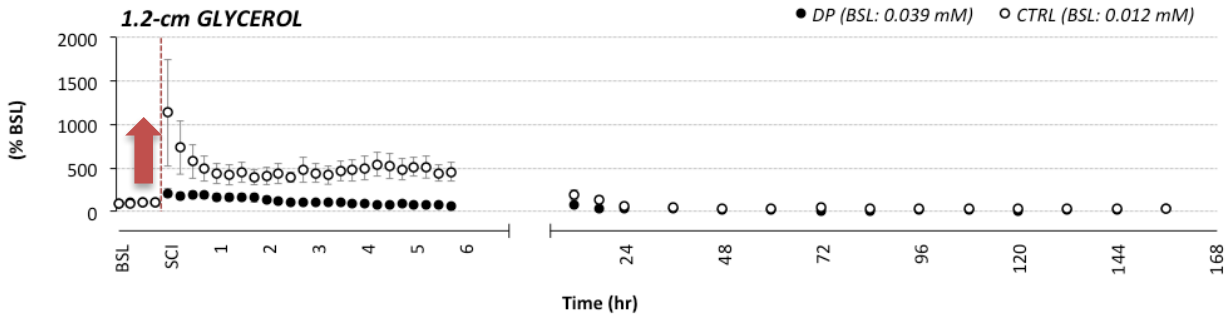
subarachnoid space to "cushion" the spinal cord during impact. To try to control for this, we aspirated the underlying CSF in both the control and the duraplasty animals to drain the CSF in the subarachnoid space immediately around the injury site just before dropping the impactor on the cord. However, this maneuver to drain the CSF from the subarachnoid space *did not* equilibrate the severity of mechanical injury. The duraplasty group demonstrated lower SCI force values at the time of impact (Table 2) with reduced microdialysis levels of glycerol, a marker of membrane damage, compared to the non-duraplasty control group. This indicated that an identical 20-cm weight drop SCI induced a different injury severity between the two groups.

Table 1. lists of surgeries performed as part of Aim 2:

SX date	Group	ID#	Name	Species	Injury details	Force (Kdyne)	BW (kg)
2016-02-09	Control	8124	Quidditch	Yucatan	**Contusion:** 50gr/20cm **Compression:** 150gr/5min	2941	24.5
2016-02-17	Control	8141	Tennis	Yucatan		3354	22.0
2016-03-08	Control	8156	UFC	Yucatan		3292	28.0
2016-03-10	Control	8157	Volleyball	Yucatan		3160	29.0
2016-03-29	Control	8065	Wrestling	Yucatan		2849	33.0
				Average		***3119***	***27.3***
				SEM		***87.5***	***1.69***

SX date	Group	ID#	Name	Species	Injury details	Force (Kdyne)	BW (kg)
2015-12-07	Duraplasty	7985	Orienteering	Yucatan	**Contusion:** 50gr/20cm **Compression:** 150gr/5min	1531	28.0
2015-12-09	Duraplasty	7983	Polo	Yucatan		2129	25.5
2016-02-11	Duraplasty	8064	Rugby	Yucatan		2242	21.5
2016-02-15	Duraplasty	8112	Soccer	Yucatan		2250	22.5
2016-03-31	Duraplasty	8140	Xare	Yucatan		1780	24.0
				Average		***2100***	***23.4***
				SEM		***85.4***	***0.68***

Figure 7: Glycerol response after SCI (2-mm). The percentage change (%Δ) is calculated using an average of 60 minutes of baseline before SCI. Compared to the control group, glutamate values of the duraplasty group were significantly ($p<0.05$) lower immediately after the weight drop. This indicates that an identical 20-cm weight drop SCI caused a different injury severity most likely due to striking the artificial graft material (duraplasty group) versus the native dura (control group).



We established that the artificial graft material itself was likely to be the source of this variability. We therefore decided to repeat this experiment but in addition to aspirating the CSF to "equilibrate" the subarachnoid spaces between the animal groups, we also planned to lay a piece of the artificial dural graft material (Dura-Matrix, Medtronic, Minneapolis, MN) on the intact dura in the non-duraplasty animals. This we felt would result in the same 'cushioning' effect.

Results:

We have now done 8 animals in which 4 non-duraplasty animals also had the dural graft placed on top of the dura just before impact. With this change, we now see relatively similar responses in glycerol (Figure 8) and impact forces (Table 2) immediately after SCI (values not significantly different). We can be more confident now that the two groups received a similar level of injury.

Figure 8: A comparison of glycerol at 0.2cm from injury between our previous group of animals (O-X) and our current group (B-I). Note the difference in y-axis scale between the graphs

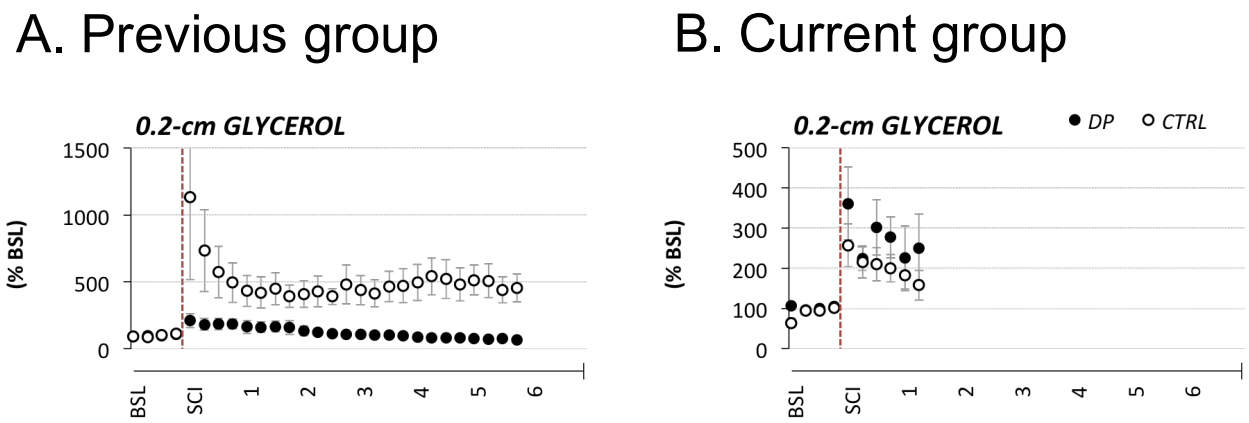


Table 3. Lists of additional surgeries performed to date:

SX date	Group	ID#	Name	Species	Injury details	Force (kdyn)	Weight (kg)	Status
2016-08-23	Control	8371	Badminton	Yucatan	**Contusion:**	3227.00	33.0	In progress
2016-09-06	Control	8372	Diving	Yucatan	50gr/20cm	2154.00	34.0	In progress
2016-09-21	Control	8437	Gymnastics	Yucatan	**Compression:** 150gr/5min	2538.00	32.0	In progress
2016-09-27	Control	8400	Heptathlon	Yucatan		2539.00	34.0	In progress
					Average	**2614.5**	**33.3**	**Not sign different**
					SEM	**223.4**	**0.5**	

SX date	Group	ID#	Name	Species	Injury details	Force (kdyn)	Weight (kg)	Status
2016-08-25	Duraplasty	8436	Croquet	Yucatan	**Contusion:**	2058.00	29.0	In progress
2016-09-11	Duraplasty	8376	Enduro	Yucatan	50gr/20cm	2116.00	34.5	In progress
2016-09-19	Duraplasty	8443	Frisbee	Yucatan	**Compression:** 150gr/5min	2043.00	34.0	In progress
2016-09-29	Duraplasty	8464	Ironman	Yucatan		2304.00	34.0	In progress
					Average	**2130.3**	**32.9**	
					SEM	**60.0**	**1.3**	

Preliminary SCBF, oxygenation and pressure data:

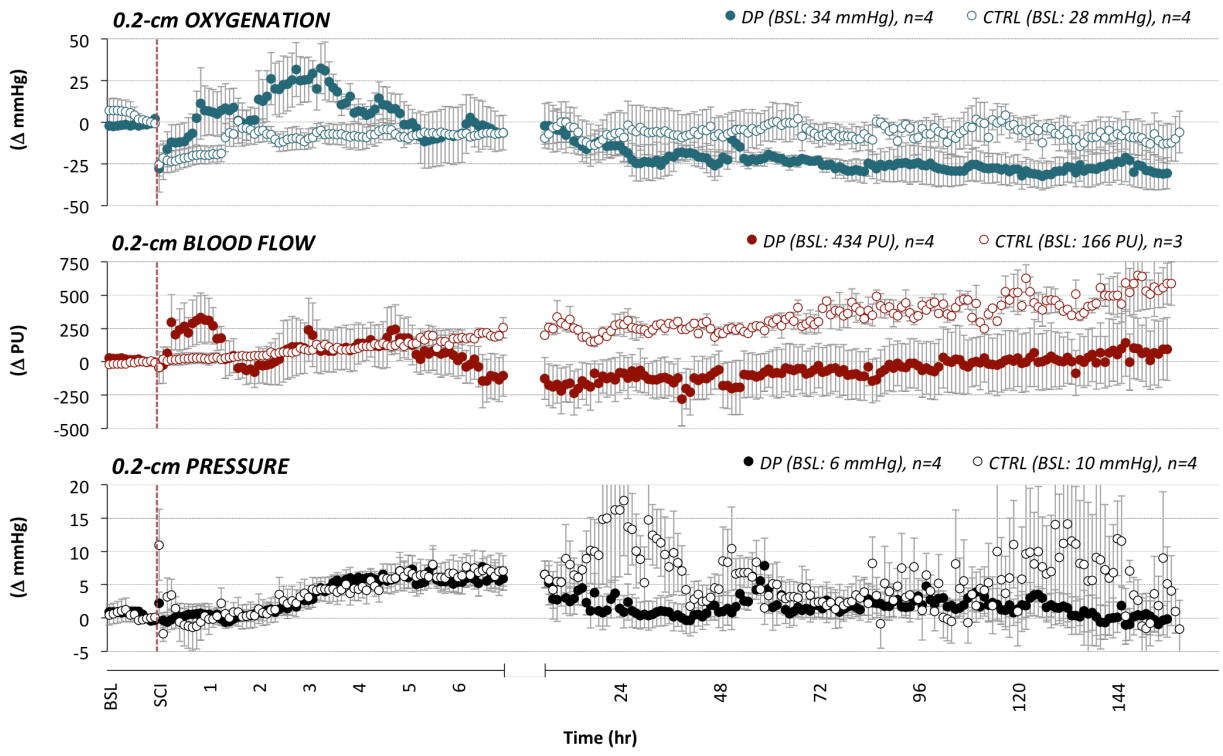
At 0.2cm from injury, we see a similar drop in oxygenation after SCI in both the duraplasty and control groups (Figure 9). There appears to be an increase in oxygenation for the duraplasty group between 2-4 hpi, however, this was only see in 2 out of 4 animals in the group (Enduro and Ironman). It may be worth noting that the increase in O2 for these two animals was accompanied by an increase in blood flow as

well. There are no major differences between the two groups over the rest of the 7 days post-SCI. The most notable difference is at the very end of the 7 days where the control group ends around an absolute value of 18mmHg and the duraplasty group ends around 4mmHg; anything below 10mmHg is considered quite anoxic.

Both duraplasty and control groups show a minor transient drop in blood flow immediately after SCI. The duraplasty group shows hyperemia after SCI compared to the control group. Post-SCI hyperemia was observed in all 4 DP animals, though at varying times after SCI. Blood flow for the duraplasty group seems to drop around 4hpi, but by 6hpi begins to rise, ending around baseline levels by 7dpi. The blood flow for the control group steadily rises over 7 days, ending around 500 units above baseline.

Immediately after SCI, the cord pressure in both groups increases. Pressure within the cord rises to 7mmHg above baseline. There is lots of noise in the pressure data, mostly cause by one animal. Pressure data tends to vary the most and is the most difficult to get 'clean' data from.

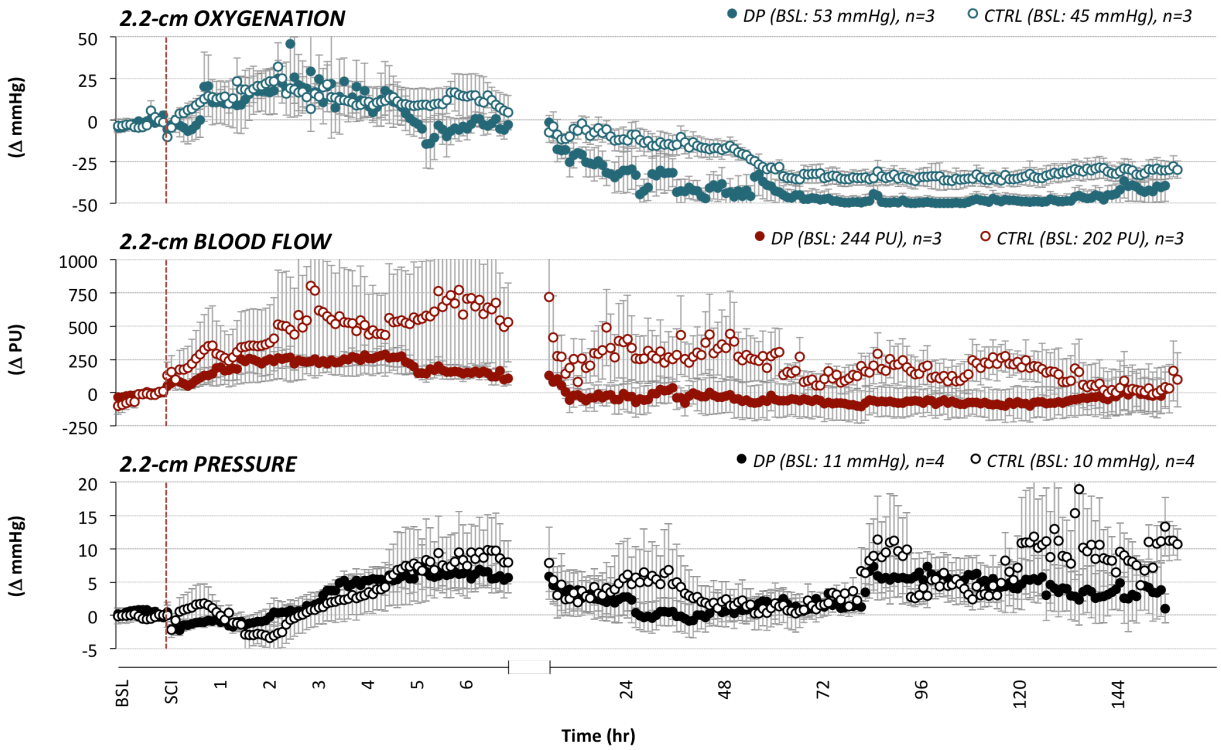
Figure 9: A comparison of the difference from baseline of oxygenation, blood flow and cord pressure at 0.2cm from the middle of the injury site, between duraplasty (filled circles) and non-duraplasty control (open circles) animals.



Further from injury (2.2-cm), we see no immediate effect of SCI on oxygenation for both groups (Figure 10). However, the duraplasty group does drop lower than the control group over the 7 days of recovery. At day 7, the average absolute values of oxygenation for the duraplasty group was ~5mmHg whereas the control group was ~15mmHg. This difference seems substantial and is similar to the contrast seen at 0.2-cm O2. It would be interesting to compare the oxygenation data with the microdialysis results.

There is no visible difference between the two groups for blood flow and cord pressure at 2.2cm from injury; both groups follow a similar trend over the 7 days of recovery. The increased blood flow within the first 6 hpi for the control group is largely driven by one animal.

Figure 10: A comparison of the difference from baseline of oxygenation, blood flow and cord pressure at 2.2cm from the middle of the injury site, between duraplasty (filled circles) and non-duraplasty control (open circles) animals.



5 KEY RESEARCH ACCOMPLISHMENTS

- Duraplasty surgery is feasible in our Porcine model of SCI
- Duraplasty surgery seems to improve functional recovery early after SCI compared to SCI-animals without duraplasty

6 CONCLUSION

Our preliminary data suggest that duraplasty surgery might improves functional recovery early after SCI. Performing a duraplasty to expand the space around the spinal cord would be a feasible neurosurgical procedure to add to the clinical spinal stabilization and decompression procedure, in the absence of other more novel neuro-regenerative treatments. In the next Year we will be conducting further studies evaluating the consequence of duraplasty on intraparenchymal spinal cord oxygenation, blood flow, and pressure, as well as, the downstream metabolic response using microdialysis. These data will further our understanding of the importance of relieving the 'intrinsic' pressure of the spinal cord to improve recovery after a traumatic SCI.

7 PUBLICATIONS, ABSTRACTS AND PRESENTATIONS

Poster presentation, Society for Neuroscience 2016, Chicago, Illinois, Nov 12-16:

DURAPLASTY IN ACUTE TRAUMATIC SCI: THE IMPACT ON METABOLISM, BLOOD FLOW, OXYGENATION, AND PRESSURE USING A PORCINE MODEL OF SCI.

N. Manouchehri[1], F. Streijger[1], K. Shortt[1], K. So[1], E.B. Okon[1], B.K. Kwon[1,2]
[1]International Collaboration of Repair Discoveries (ICORD), University of British Columbia, Vancouver, BC, Canada; [2]Vancouver Spine Surgery Institute, Department of Orthopaedics, University of British Columbia, Vancouver, BC, Canada

Abstract (max 2300 characters):
After traumatic spinal cord injury (SCI), secondary pathophysiologic processes and damage result in worsening the extent of the primary injury and ultimately functional outcome. One commonly observed secondary injury phenomenon in the acute injury period is progressive edema and swelling of the spinal cord. This may increase intraparenchymal spinal cord pressure as the cord swells and is compressed against the dura, resulting in a compromise in perfusion. One way to potentially alleviate these effects is to expand the subarachnoid space by performing a duraplasty, which could potentially reduce intraparenchymal pressure and improve perfusion. Therefore, in this study, we determine the effect of expansive duraplasty on intraparenchymal pressure, cerebrospinal fluid pressure, blood flow, oxygenation, and metabolic responses in a porcine model of SCI.

Female Yucatan miniature pigs received a T10 contusion-compression SCI either with or without expansion duraplasty using an artificial dural graft. For the SCI-only animals the dura was left intact. Prior to injury, probes for microdialysis, blood flow (SCBF), oxygenation ($PaPo_2$), and hydrostatic pressure measurements were inserted into the spinal cord 0.2 and 2.2 cm from the injury site. Measurements occurred for 4 hours post-injury, after which the animals were recovered for continued monitoring over 7 days.
Contusion-compression SCI resulted in decreased SCBF levels close to the injury site (0.2-cm location) followed by a subsequent increase during the following days. Similarly, $PaPO_2$ plummeted immediately after injury and these levels remained low for the entire 7 day period post-injury The L/P ratio increased within minutes, with a second continual increase at day 3. A gradual increase in L/P ratio was also observed at 2.2cm. Hydrostatic pressure remained consistently elevated for days and negatively correlated with changes in SCBF. An imbalance between SCBF and tissue metabolism was also observed, resulting in metabolic stress and insufficient oxygen levels.
The next step is to determine if expansion duraplasty can alleviate the observed increase in pressure and ischemia/hypoxia following SCI, a study that is currently being performed. Our preliminary data on 4 pigs shows promise, demonstrating the feasibility of the duraplasty technique and an enlargement of the dorsal subarachnoid space under the duraplasty. Microdialysis, blood flow, oxygenation, and hydrostatic pressure measurements are presently being analyzed.

Session Type: Poster
Session Number: 323
Session Title: Spinal Cord Injury Models and Mechanisms
Date and Time: Monday Nov 14, 2016 8:00 AM - 12:00 PM
Location: San Diego Convention Center: Halls B-H
Abstract Control Number: 14632

8 INVENTIONS, PATENTS AND LICENSES

Nothing to report

9 REPORTABLE OUTCOMES

Nothing to report

10 OTHER ACHIEVEMENTS

Nothing to report

11 REFERENCES

Jones CF, Cripton PA, Kwon BK (2012) ***Gross morphological changes of the spinal cord immediately after surgical decompression in a large animal model of traumatic spinal cord injury.*** Spine (Phila Pa 1976); 37(15): E890-9. PMID: 22433504.

12 APPENDICES

None

13 FINANCIAL HEALTH

FMS GL Summary - Extracted on 21-OCT-2016 08:34 AM																
Report Parameters: Fund [R4300] Dept [177000] Program [] Project [17R21883]																
Date Range: From NOV-2015 to OCT-2016																
PG Year End: SEP																
	Funding Allo	Actual Expenditures														Commitments
Description	YTD	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Period Total	PG YTD	YTD
Net Assets-Research-Restricted	-72,272.72	0	0	0	0	0	0	0	0	0	0	0	0	**0**	-82,416.98	0
Sub Total	-72,272.72	0	0	0	0	0	0	0	0	0	0	0	0	**0**	-82,416.98	0
Grants-US government	0	0	0	0	-145,022.02	0	0	0	0	0	-135,135.84	0	0	**-280,157.86**	0	0
Sub Total	0	0	0	0	-145022.02	0	0	0	0	0	-135135.84	0	0	**-280,157.86**	0	0
Budget Balance Carry Forward	390,829.83	0	0	0	0	0	0	0	0	0	0	0	0	**0**	0	0
Budget pool-Expense	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**	0	0
Salaries-Students(Instruc&Res)	0	1,750.00	-563.15	207.9	207.9	207.9	207.9	207.9	103.95	0	0	0	0	**2,330.30**	0	0
Salaries-Staff	0	3,035.68	3,217.84	-26,981.40	3,066.04	7,748.04	3,066.04	3,079.84	3,079.84	3,095.24	3,095.24	3,095.24	0	**8,597.64**	0	0
Employee benefits-Main	0	567.78	553.8	-3,208.72	570.03	570.1	570.02	572.27	571.8	573.83	573.84	573.84	0	**2,488.59**	0	0
Employee benefits-insurance	0	21.24	21.46	21.46	21.46	21.46	21.46	21.56	21.56	21.66	21.66	21.66	0	**236.64**	0	0
Couriers	0	0	0	0	0	104.24	0	16.1	0	0	0	379.51	0	**499.85**	0	0
Customs & freight	0	0	0	30.78	32.05	140.32	0	0	0	0	0	120.05	0	**323.2**	0	0
Technical supplies	0	813.9	785.85	12,872.94	5,117.60	9,221.11	515.81	766.63	0	0	8,218.13	4,763.55	10,095.75	**53,171.27**	10,095.75	-6,063.91
Laboratory supplies	0	0	0	0	0	0	0	94.47	0	0	0	161.22	0	**255.69**	0	0
Animal costs	0	12,943.38	4,477.60	19,812.18	765	42,925.90	0	3,230.00	0	0	22,528.25	30,836.14	41,207.50	**178,725.95**	41,207.50	0
Bank charges	0	0	0	7	1.2	14	0	0	0	10.33	0	0	0	**32.53**	0	0
Rentals-Equipment	0	0	0	0	0	10,330.66	0	0	0	4,658.95	0	0	0	**14,989.61**	0	0
Membership fees	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**	0	0
Prof fees-IndividualsT4A	0	0	935	0	0	0	0	0	0	0	0	0	0	**935**	0	0
Overhead	0	2,923.84	1,757.09	-16,298.65	2,102.80	4,649.84	2,102.79	2,111.57	2,054.77	2,007.76	2,007.76	2,007.76	0	**7,427.33**	0	0
Sub Total	390,829.83	22,055.82	11,185.49	-13,536.51	11,884.08	75,933.57	6,484.02	10,100.34	5,831.92	10,367.77	36,444.88	41,958.97	51,303.25	**270,013.60**	51,303.25	-6,063.91
Total Expenses:	390,829.83	22,055.82	11,185.49	-13,536.51	11,884.08	75,933.57	6,484.02	10,100.34	5,831.92	10,367.77	36,444.88	41,958.97	51,303.25	**270,013.60**	51,303.25	-6,063.91
														Balance Available:	**345,590.49**	